Abdominal Ultrasonographic Findings and Gallbladder Wall Thickening in Children with Infectious Mononucleosis Caused by Epstein-Barr Virus: Clinical-Ultrasonographic Correlation

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Directed by Professor Choon Sik Yoon

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Table of Contents

List of Figures

List of Tables

Abstract

Abdominal Ultrasonographic Findings and Gallbladder Wall Thickening in Children with Infectious Mononucleosis Caused by Epstein-Barr Virus: Clinical-Ultrasonographic Correlation

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Infectious mononucleosis syndrome may be presented with various clinical courses, but there is no known severity or prognostic index available. We used sonography to measure gallbladder wall thickness in pediatric patients with infectious mononucleosis syndromes caused by Epstein-Barr virus (EBV) and then evaluated laboratory data, and clinical evolution to assess any relationship between gallbladder wall thickening (GBWT) and the severity of disease.

We retrospectively reviewed the medical records and ultrasonographies of 84 patients with infectious mononucleosis who were admitted to pediatric clinics between January 2001 and December 2004. Patients fulfilled clinical triad of infectious mononucleosis syndromes on the basis of fever, tonsillopharyngitis, and cervical lymphadenopathy, and showed positive serology for EBV. 19 patients were excluded who had positive serologic results for mycoplasma and hepatitis virus antibodies. Total 65 patients were included

in this study. The gallbladder wall thickness in each patient was sonographically determined. GBWT was defined as a wall thickness exceeding 3 mm. We assessed the laboratory data and clinical evolution in each patient, and the differences between patients with and without GBWT were statistically analyzed.

GBWT was observed in 24 (34%) of the 65 patients. The mean duration of hospitalization for the patients with GBWT (10 days ± 3.5) was significantly longer than for those without GBWT (6 days ± 2.3; $p < 0.05$). The total bilirubin level in the patients with GBWT (1.2 mg/dl ± 1.8 mg/dl) was significantly higher than in the patients without GBWT (0.3 mg/dl ± 0.2 mg/dl; $p < 0.05$). Aspartate aminotransferase (AST) level was significantly higher in patients with GBWT (267 mg/dl ± 332 mg/dl) than those without GBWT (80 mg/dl ± 83mg/dl; $p < 0.05$). And, alanine aminotransferase (ALT) level was also higher in patients with GBWT (249 mg/dl ± 284 mg/dl) than patients without GBWT (90 mg/dl ± 102 mg/dl; $p < 0.05$). The total protein, serum albumin, and alkaline phosphatase (ALP) levels were not significantly as also significantly different between two groups. The two groups did not differ significantly in the mean white blood cell (WBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) levels.

GBWT in mononucleosis syndromes may be a sign of the severity of the illness and when present indicates the need to carefully monitor the clinical course.

Key words: infectious mononucleosis, Epstein-Barr virus (EBV), gallbladder wall thickening, ultrasonography

I. Introduction

Infectious mononucleosis syndrome is characterized by fever, tonsillopharyngitis, and cervical lymphadenopathy.[1] The Epstein-Barr virus (EBV) is a typical pathogenic agent of infectious mononucleosis; other organisms that cause mononucleosis syndromes include cytomegalovirus (CMV), Toxoplasma gondii, human immunodeficiency virus (HIV) type 1, human herpesvirus-6, rubivirus, hepatitis viruses, and adenoviruses.[1,2] EBV infectious mononucleosis is often subclinical, and the only manifestation of EBV infection is serological response to EBV surface proteins with serological tests.[1,2] Infectious mononucleosis is a typical self-limited lymphoproliferative illness in adolescents and young adults; however, in a select group of patients, infectious mononucleosis may follow an aggressive course and result in life-threatening complications.

Infectious mononucleosis may be characterized by high fever, pain in the right upper quadrant of the abdomen, and a positive Murphy sign, which are indistinguishable from the pain caused by cholecystitis.[3-7] In infectious mononucleosis patients, splenomegaly is the most common finding and is observed in over 50%.[8] Other ultrasonographic findings include hepatitis, mesenteric lymphadenopathy, hyperplasia of gut-associated lymphoid tissue, pancreatitis, and ascites.[9-10]

The literature indicates that gallbladder wall thickening (GBWT) in patients with infectious mononucleosis is very rare, with only case reports published.[3-7,10] Although GBWT in infectious mononucleosis is rare and clarification of the pathogenesis of GBWT in infectious mononucleosis requires

further study, such finding has been considered an ominous sign associated with serious complications such as pulmonary edema requiring intensive care and severe hepatic dysfunction.[5,6] In contrast, one elderly group study announced that the mean hospital stay was longer in the patients with gallbladder wall thickening than in those without gallbladder thickening, and associated with severity of the illness.[11] In addition, this study also indicated that gallbladder wall thickening was not rare in infectious mononucleosis (15%).

The association between gall bladder wall thickening and clinical significance has not been well documented, and even in children. In this study, we used ultasonography to measure gallbladder wall thickness in children with mononucleosis syndromes, and then evaluated laboratory data and clinical evolution to assess any relationship between gall bladder wall thickening and the severity of the disease.

II. Materials and Methods

A. Patient Selection

We retrospectively reviewed 84 consecutive patients admitted to pediatric clinics in our hospital with infectious mononucleosis between January 2001 and December 2004. Of 84 patients, 19 patients were excluded who showed positive results on serologic tests for mycoplasma antibody (17 cases) and hepatitis virus (2 cases). All 65 patients had no evidence of gallbladder stones, adenomyomatosis, gallbladder tumors, or chronic liver disease, which could affect the sonographic appearances of the gallbladder. The patients are comprised of 27 males and 38 females, with a mean age ± standard deviation (SD) of 8 ± 4 years (range, 2–14 years). All of the children fulfilled the clinical criteria of fever, tonsillopharyngitis, and cervical lymphadenopathy. Serology was used for the confirmation of EBV as a causative organism.

B. Clinical Evaluation

We meticulously reviewed all the medical records available. Hospital stay, accompanied symptoms and signs were evaluated. All the patients met the classic triad of EBV infectious mononucleosis; fever, pharyngitis, and cervical lymphadenopathy. Other symptoms and signs were assessed, especially life-threatening conditions, such as neurologic, pulmonary, and hematologic complications.

C. Laboratory Analyses

On the day of the ultrasonographic examination, blood studies were

performed to measure the patients' white blood cell (WBC) count and levels of atypical lymphocytes, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), total protein, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). We assessed the relationship between the gallbladder wall thickness and these laboratory findings.

D. Ultrasonography Examination

Patients underwent abdominal ultrasonography on admission or the day after admission. Follow-up ultrasonographies were performed during admission in case of severe clinical deterioration, such as aggravation of jaundice, sepsis, or neurologic symptoms.

Abdominal Ultrasonography was performed using an ACUSON 128XP/10 ultrasound scanner (Acuson, Mountain view, California) and a 4.0 MHz convex-array and 7.0 MHz linear transducers. The gallbladder wall thickness in each patient was measured on longitudinal and transverse subcostal and intercostals sonograms. A gallbladder wall thickness greater than 3 mm was defined as abnormal gallbladder wall thickening.

The measurement of spleen length was the optically maximal distance (ideally at the hilum) on the longitudinal coronal view (between the most superomedial and the most inferolateral points).[12] We compared the ultrasonographic findings between two groups, and assessed any significant differences in addition to GBWT.

E. Statistical Analysis

The differences between the patients with GBWT and those without GBWT were analyzed using the unpaired Student's *t*-test. Values were

expressed as mean ± SD. A p value less than 0.05 was considered statistically significant. In addition, clinical manifestation and evolution, such as physical findings, hospital stay, and complications, were analyzed in the two groups.

III. Result

Demographic, laboratory, and ultrasonographic findings in 65 infectious mononucleosis syndrome patients were shown in the Table.1.

There was no significant difference between the patients with GBWT and those without GBWT in age or sex. All the patients were symptomatic with fever, pharyngitis, and cervical lymphadenopathy. Patients also showed various gastrointestinal (abdominal pain, hepatosplenomegaly, indigestion, jaundice) and musculoskeletal (arthralgia, myalgia) symptoms and signs. The mean duration of hospitalization for the patients with GBWT (10 ± 3.5 days) was significantly longer than for those without GBWT (6 ± 2.3 days; $p < 0.05$). Though the results were not shown in the table, three out of 24 patients with GBWT followed aggressive clinical course; severe hepatic dysfunction and failure (2 cases) and sepsis (1 case). But, there was no case of pulmonary edema.

The total bilirubin level in the patients with GBWT (1.2 mg/dl ± 1.8 mg/dl) was significantly higher than in the patients without GBWT (0.3 mg/dl ± 0.2 mg/dl; $p < 0.05$). AST level was significantly higher in patients with GBWT (267 mg/dl ± 332 mg/dl) than in those without GBWT (80 mg/dl ± 83 mg/dl). And, ALT level was also higher in patients with GBWT (249 mg/dl ± 284 mg/dl) than in patients without GBWT (90 mg/dl ± 102 mg/dl). The total protein, serum albumin, and ALP levels were not significantly different between two groups. The two groups did not differ significantly in the mean WBC, CRP, and ESR levels.

Ultrasonographies were performed on the day of admission or on the

day after. The most common abdominal ultrasonographic finding was splenomegaly (36 cases; 55%), and other findings included GBWT (24 cases; 34%), hepatomegaly (13 cases; 20%), increased periportal echogeneity (11 cases; 15%), lymph node enlargement at porta hepatis, peripancreatic, and mesenteric areas (7 cases; 11%), and ascites (2 cases; 3%). The incidences of each group are listed in the table.

Table-1. Demographic, Laboratory, and Ultrasonographic Findings in 65 Infectious Mononucleosis Syndrome Patients.

Findings	With GBWT (n=24)	Without GBWT (n=41)
Patient age, years	8 ± 4	5 ± 4
Male-to-female ratio	10 : 14	17 : 24
Duration of hospitalization, days	10 ± 3.47†	6 ± 2.28†
WBC count, cells/µl	11.7 ± 9.6	10.9 ± 6.9
Differential ratio of leukocytes, %	46.2 ± 27.57	52.9 ± 24.0
Differential ratio of lymphocytes, %	41.1 ± 23.80	36.2 ± 20.3
CRP, mg/dl	38.7 ± 81.8	33.0 ± 36.6
ESR, mg/dl	29.7 ± 17.4	29.4 ±15.1
Total bilirubin, mg/dl	1.2 ±1.8†	0.3 ± 0.2†
AST, IU/l	267 ± 332†	80 ± 83†
ALT, IU/l	249 ± 284†	90 ± 102†
ALP, IU/l	310 ± 139	240 ± 139
Total protein, g/dl	6.5 ± 0.5	6.7 ± 0.3
Albumin, g/dl	3.5 ± 0.4	4.0 ± 0.3
Splenomegaly	16 (67%)	20 (50%)
Hepatomegaly	7 (29%)	6 (15%)
Increased liver periportal echogeneity	6 (25%)	5 (13%)
Lymph node enlargement	3 (13%)	4 (10%)
Ascites	2 (8%)	0

Abbreviations: GBWT, gallbladder wall thickening; WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

*Values are expressed as mean ± standard deviation.

† $p < 0.05$ compared with the group without GBWT.

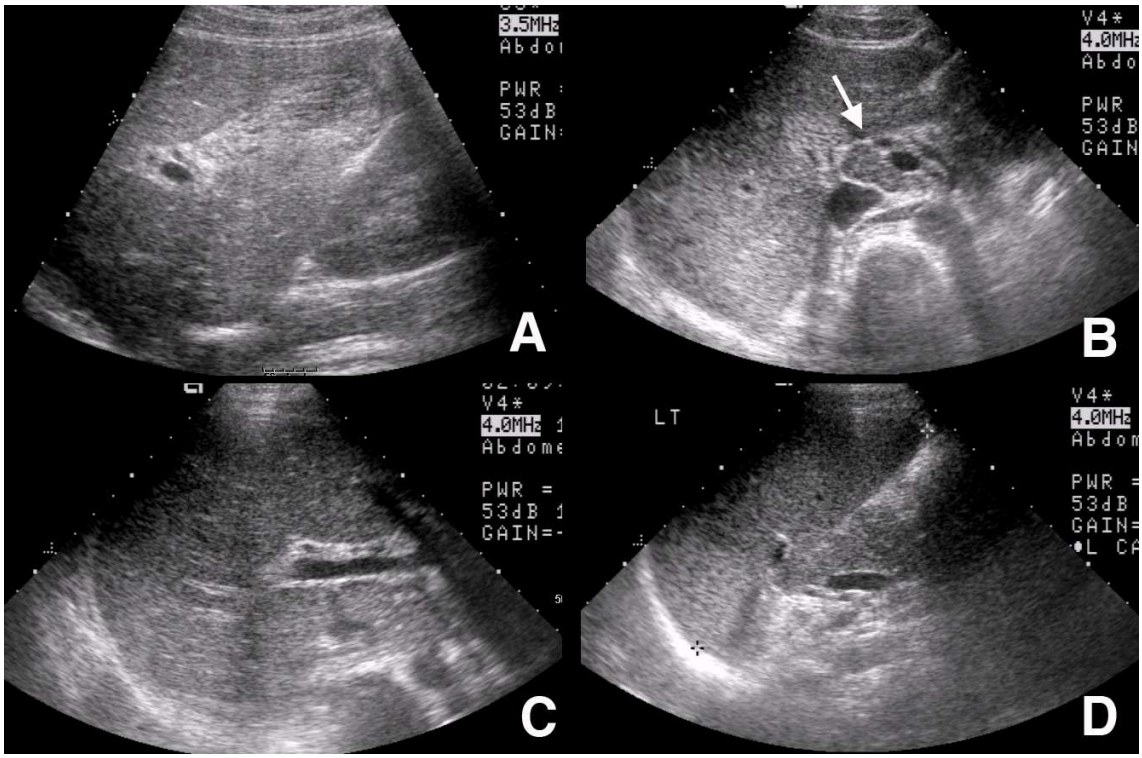

Figure.1 - Abdominal ultrasonography of a 13-year-old female with infectious mononucleosis. **A.** Gallbladder shows diffuse mural thickening. **B.** Lymphadenopathy is note at porta hepatis. **C.** Liver shows increased periportal echogeneity. **D.** Spleen is enlarged.

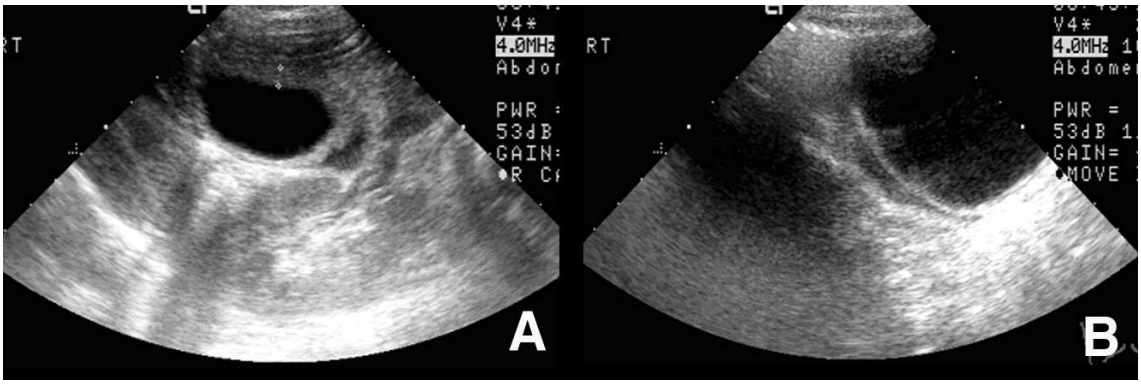

Figure.2 - Abdominal ultrasonography of a 5-year-old male with infectious mononucleosis. **A.** Ultrasonography shows diffuse gallbladder wall thickening. **B.** Fluid collection is noted in pelvic cavity.

IV. Discussion

Infectious mononucleosis is a disease resulting from an infection of the lymphatic system caused by various organisms, and classical triad is fever, tonsilopharyngitis, and cervical lymphadenopathy. Infectious mononucleosis is a typical self-limited lymphoproliferative illness in adolescents and young adults; however, in a select group of patients, infectious mononucleosis may follow an aggressive course and result in life-threatening complications. However, to the best of our knowledge, there is no known severity or prognostic index available for such patients who may follow various clinical outcomes both clinically and radiologically.

Ultrasonography is very convenient and harmless modality for the children, although the performance is operator-dependant. In 65 patients, the most frequent ultrasonographic finding except GBWT in patients with infectious mononucleosis was splenomegaly (55%) (Fig.1). Incidence of splenomegaly was higher in the patients with GBWT, but not a distinct feature. The literature indicated that splenomegaly was very common in this disease group and splenic rupture was a common cause of death.[8-10] But, there were no cases of splenic rupture in this study. The other ultrasonographic findings included hepatomegaly (20%), increased periportal echogeneity (15%), enlarged lymph nodes at porta hepatic, peripancreatic, and mesenteric areas (11%), and ascites (2%) (Fig.1, Fig.2).

GBWT, which was of our concern, is observed in an array of conditions, including acute or chronic cholecystitis, acute viral hepatitis, chronic liver

disease, congestive heart failure, chronic renal failure, hypoalbuminemia, and acquired immune deficiency syndrome, as well as in the postprandial state.[13,14] But, GBWT is not a common feature in patients with infectious mononucleosis, and its clinical significance is still unclear.[3-7,10] We found GBWT in 34% of our patients with infectious mononucleosis syndromes. This incidence was much lower than that found in patients with viral hepatitis (91~98%), however, was higher than that reported in the literature.[15,16] In this study, initial ultrasonographic examinations were performed routinely irregardless of severities of symptoms and signs. Consequently, routine and careful examination could detect GBWT in infectious mononucleosis syndromes more frequently. However, our study may not represent the true incidence of GBWT in patients with infectious mononucleosis, which was one of the limitations in our study that will be discussed later.

The pathogenesis of gallbladder wall thickening in infectious mononucleosis is disputed, but several hypotheses have been advanced: direct involvement of the wall with infected lymphocytes, severe hypoproteinemia, lymphatic obstruction by enlarged nodes at the porta hepatis, and an immunologic reaction similar to that which occurs in viral hepatitis.[6,7]

GBWT in infectious mononucleosis syndromes has been considered an ominous sign associated with serious complications such as pulmonary edema requiring intensive care and severe hepatic dysfunction.[5,6] In our study, the levels of total bilirubin, AST, and ALT were significantly higher in patients with GBWT, and the mean hospitalization days were also statistically longer; An elderly group report showed a similar result; in which the incidence of GBWT was 15%.[11] Our result also suggested that GBWT in patients with infectious

mononucleosis was related to longer disease duration and hepatic dysfunction. GBWT in mononucleosis syndromes may be a sign of the severity of the illness and when present indicates the need to carefully monitor the clinical course.

The true incidence of GBWT may differ from that of our study. Because we only focused on symptomatic inpatients admitted to pediatric clinics, the incidence of GBWT in outpatients was not reflected in our result. And it is possible to have missed those with subclinical infectious mononucleosis who did not undergo ultrasonography, though ultrasonography was performed routinely for all suspicious patients. Furthermore, 19 patients, who were excluded in the study planning, showed positive serology for both mycoplasma and EBV antibodies. Interestingly, most of these patients underwent severe hepatic dysfunction and showed GBWT frequently. In this sense, the incidence of GBWT would change when it comes to all causative organisms beside EBV.

Another limitation of this study was the fact that follow-up ultrasonography was not available during recovery. In one literature, all patients with GBWT on initial ultrasonographies were reported to show resolution of GBWT as hepatic function improved.[11] If GBWT is related to worse clinical course, further study should be focused on the relationship between the resolution of GBWT and recovery of the disease.

V. Conclusion

Infectious mononucleosis syndrome may be presented with various clinical courses, but there is no known severity or prognostic index available. GBWT in mononucleosis syndromes children may be related to severity of the illness and hepatic dysfunction, and indicate the need to carefully monitor the clinical course when present.

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Abstract in Korean

EBV 감염에 의한 감염성 단핵구증 소아의 복부 초음파 소견 및 담낭벽 비후: 임상적-초음파 소견의 연관성

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이 재 훈

목적: 저자는 Epstein-Barr Virus (EBV) 감염에 의한 감염성 단핵구증 환아에서 복부초음파로 담낭벽의 두께를 측정하고, 혈액검사 소견, 임상 양상들을 비교-분석하여, 담낭벽 비후 소견과 질환의 중증도에 대한 관계를 연구하고자 한다.

연구방법: 본 연구는 2001년 1월부터 2004년 12월에 걸쳐 감염성 단핵구증으로 본원 소아과에 입원환 환아 84명을 대상으로 하였다. 총 84명의 환아들의 의무기록 및 복부초음파 소견을 후향적으로 고찰하였다. 환아들은 모두 감염성 단핵구증의 특징적 양상인 발열, 인후염, 그리고, 경부림프절비대를 가지고 있었으며, EBV에 대한 혈청학적 검사에 대하여 양성을 보인 환아를 연구에 포함시켰다. 이들 중 마이코플라스마와 간염 바이러스에 양성을 보인 19명의 환아는 제외되었다. 총 65명의 환아가 최종적으로 연구에 포함되었다.

담낭벽 두께는 복부초음파로 측정하였으며, 담낭벽 비후는 그 두께가 3mm 넘는 경우로 정의하였다. 저자들은 혈액검사소견 및 질환의 경과를 살펴보았으며, 담낭벽 비후 소견을 보이는 환아 군과 보이지 않는 환아 군 사이에서 유의한 차이점을 보이는 항목들을 연구하였다.

결과: 담낭벽 비후 소견은 65명 중 24명(34%)의 환아에서 관찰되었다. 평균 입원 일수는 담낭벽 비후를 보인 군에서 그렇지 않은 군보다 유의하게 길었다 (10 ± 3.5 vs 6 ± 2.3; $p < 0.05$). 총빌리루빈 수치 또한 담낭벽 비후소견을 보인 환아들에게서 유의하게 높았다 (1.2 mg/dl ± 1.8 mg/dl vs 0.3 mg/dl ± 0.2 mg/dl; $p < 0.05$). 그리고, Aspartate aminotransferase (AST) 수치도 담낭벽 비후소견을 보이는 환아들에서 높았으며 (267 mg/dl ± 332 mg/dl vs 80 mg/dl ± 83mg/dl; $p < 0.05$), alanine aminotransferase (ALT) 수치도 같은 결과를 보였다 (249 mg/dl ± 284 mg/dl vs 90 mg/dl ± 102 mg/dl; $p < 0.05$). 그러나, 총단백질, 혈청 알부민, alkaline phosphatase (ALP), 백혈구 수치, C-reactive protein (CRP), 그리고, erythrocyte sedimentation rate (ESR) 수치는 두 군 간에 통계적으로 유의한 차이는 없었다.

결론. EBV 감염에 의한 감염성 단핵구증 환아에서 관찰되는 담낭벽 비후소견은 질환의 중증도와 상관관계가 있으며, 그러한 소견을 보이는 환아에서는 보다 면밀한 임상관찰이 요구된다.

핵심단어 : 감염성 단핵구증, Epstein-Barr virus (EBV), 담낭벽 비후, 초음파